Fecal Microbiota Transplant Decreases Mortality in Patients with Refractory Severe or Fulminant *Clostridioides difficile* Infection

Short title: FMT decreases mortality in refractory CDI

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Abbreviations: CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; ICU, intensive care unit; IBD, inflammatory bowel disease; LOS, length of stay; SFCDI, severe or fulminant CDI; WBC, white blood cell

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Abstract:

Background & Aims: Fecal microbiota transplantation (FMT) is recommended for recurrent *Clostridioides difficile* infection (CDI). FMT cures nearly 80% of patients with severe or fulminant CDI (SFCDI) when utilized in a sequential manner. We compared outcomes of hospitalized patients before and after implementation of an FMT program for SFCDI and investigated whether the changes could be directly attributed to the FMT program.

Methods: We performed a retrospective analysis of characteristics and outcomes of patients hospitalized for SFCDI (430 hospitalizations) at a single center, from January 2009 through December 2016. We performed subgroup analyses of 199 patients with fulminant CDI and 110 patients with refractory SFCDI (no improvement after 5 or more days of maximal anti-CDI antibiotic therapy). We compared CDI-related mortality within 30 days of hospitalization, CDI-related colectomy, length of hospital stay, and readmission to the hospital within 30 days before (2009–2012) vs after (2013–2016) implementation of the inpatient FMT program.

Results: CDI-related mortality and colectomy were lower after implementation of the FMT program. Overall, CDI-related mortality was 10.2% before the FMT program was implemented vs 4.4% after (*P*=.02). For patients with fulminant CDI, CDI-related mortality was 21.3% before the FMT program was implemented vs 9.1% after (*P*=.015). For patients with refractory SFCDI, CDI-related mortality was 43.2% before the FMT program vs 12.1% after (*P* < .001).
The FMT program significantly reduced CDI-related colectomy in patients with SFCDI (6.8% before vs 2.7% after; *P*=.041), in patients with fulminant CDI (15.7% before vs 5.5% after; *P*=.017), and patients with refractory SFCDI (31.8% vs 7.6%; *P* = .001). The effect of FMT program implementation on CDI-related mortality remained significant for patients with refractory SFCDI after we accounted for the underlying secular trend (odds ratio, 0.09 for level change; *P*=.023).

Conclusions: An FMT program significantly decreased CDI-related mortality among patients hospitalized with refractory SFCDI.

KEY WORDS: gut microbe, dysbiosis, bacteria, treatment

What You Need to Know

Background: Fecal microbiota transplant (FMT) is an effective treatment for severe or fulminant *Clostridioides difficile* infection (SFCDI). We compared outcomes of hospitalized patients before vs after implementation of an FMT program for SFCDI and investigated whether changes could be directly attributed to the FMT program.

Findings: In a comparison of 430 hospitalized patients with SFCDI, we found that a subgroup of patients with SFCDI that was refractory to maximum antibiotic treatment for 5 or more days had a significant decrease in CDI-related mortality after the FMT program began, after we accounted for demographic features.

Implications for patient care: FMT should be considered for patients hospitalized for refractory SFCDI.

Introduction

Clostridioides difficile is the leading cause of nosocomial diarrhea in the world.[1,2] Approximately 8% of patients with *Clostridioides difficile* infection (CDI) develop severe or fulminant (formerly severe-complicated) disease leading to an elevated risk for toxic megacolon, multi-organ failure, and mortality.[3]

The Infectious Disease Society of America (IDSA) recommends vancomycin as first-line therapy for all categories of CDI severity,[4] while surgery should be considered for severe or fulminant CDI (SFCDI) refractory to maximum medical therapy.[5] Despite improvements in surgical technique,[6] clinical prediction models for poor surgical outcomes,[7] and conceptual changes in the timing of surgery,[8,9] 30-day post-colectomy mortality rates are upwards of 40%.[10,11]

Fecal microbiota transplantation (FMT) is recommended therapy for recurrent CDI, with cure rates above 80%,[12-17] and decreased relapse compared to anti-CDI antibiotic therapy.[15,18,19] Several studies have also demonstrated FMT's efficacy in treating SFCDI, with 91% cure for severe CDI and 66% for fulminant CDI.[20] Cure rates for fulminant CDI increase to nearly 90% when FMTs are performed in a sequential manner in combination with vancomycin.[21,22] More importantly, medical centers in Italy and France report decreasing mortality and colectomy rates in SFCDI after FMT availability.[23,24]

This study aimed to evaluate changes in patient outcomes before and after implementation of an FMT program for patients hospitalized with SFCDI, and to determine if such changes could be directly attributed to the FMT program.

Materials and Methods

Data Collection

This retrospective cohort study included hospitalized adults (age ≥18 years) with a diagnosis of severe or fulminant CDI between January 2009 and December 2016 at Indiana University Hospital. Hospital admissions with ICD-9 008.45 and ICD-10 A04.7 diagnosis codes were identified from an institutional electronic medical record system (Cerner) and additional data collected via individual chart review. This study was approved by the Institutional Review Board at Indiana University. Patient characteristics included age at the time of hospitalization, sex, Charlson Comorbidity Index,[25] immunocompromised state, and underlying inflammatory bowel disease (IBD). CDI characteristics included white blood cell count, serum albumin concentration, number of previous CDI episodes, as well as evidence of CDI-related end-organ damage such as hypotension, vasopressor use, mental status change, acute kidney injury, ileus, toxic megacolon, mechanical ventilation, and/or admission to the intensive care unit (ICU). Finally, FMT-related variables were also recorded including donor type (patient-selected versus universal), method of delivery (enema versus colonoscopy), number of FMTs performed during hospitalization, and presence of pseudomembranous colitis at time of colonoscopy.

Definitions

We classified CDI into severe CDI or fulminant CDI based on the IDSA guidelines.[4] We defined refractory SFCDI as patients with severe or fulminant CDI who failed to respond (progressive worsening or no significant improvement in objective clinical parameters such as leukocytosis, diarrhea, hypotension, vasopressor requirement) to maximum anti-CDI antimicrobial therapy via PO vancomycin

for at least 5 days. In the event of ileus and/or toxic megacolon, rectal vancomycin and IV metronidazole were also included in the regimen.

FMT Treatment Protocol

After inpatient FMT program availability in 2013, patients with SFCDI were offered FMT if they had evidence of refractory SFCDI or had ≥2 recurrences of CDI. Patients with refractory SFCDI received our previously published inpatient sequential FMT protocol, which combines oral vancomycin and pseudomembrane-driven sequential FMT(s).[26] The treatment algorithm can be found in **Supplementary materials**. The majority of our patients received frozen-thawed stool provided by a stool bank (OpenBiome, Cambridge, MA, USA), which employs a standardized and rigorous screening process for donors.[27]

Outcomes

Patients were grouped into a pre-FMT (2009-2012) and post-FMT (2013-2016) time period. Additionally, we performed analyses on two subgroups of patients: 1) fulminant CDI patients and 2) refractory SFCDI patients.

The primary study outcome was 30-day CDI-related mortality (in-hospital death and death within 30 days post-discharge were variables captured by institutional medical records and our prospectively collected FMT database). Secondary outcome measures included CDI-related colectomy during hospitalization, length of stay (LOS), and 30-day readmission. Re-admissions were documented and treated as a distinct admission event. Hospitalizations with in-hospital patient death were excluded from the analysis of 30-day readmission. This resulted in a total of 72 SFCDI hospitalizations being excluded for the analysis of 30-day readmission, including 52 fulminant CDI hospitalizations, and 36 refractory SFCDI hospitalizations. The clinical course of each patient who died or underwent colectomy was reviewed to determine whether the event was CDI-related.

Statistical Analysis

Patient and disease characteristics at the time of hospital admission were summarized using mean values with standard deviation or median values with interquartile range (25^{th} to 75^{th} percentile) for continuous variables; proportions were used for categorical values. To compare patient characteristics before and after FMT program implementation, the two-sample t-test or Wilcoxon rank sum test was used for continuous variables while Pearson's chi-square test or Fisher's exact test was used for categorical variables. Differences in outcomes between the pre- and post-FMT time periods were compared in a similar fashion.

Segmented logistic regression (SLR) was used to evaluate whether differences in outcomes between time periods could be attributed to FMT program implementation or were due to secular changes (eg changes that would have happened even without the FMT program). Specifically, separate intercepts and slopes are quantified in each time period and the effect of the FMT program is then indicated by the differences in intercept and/or slope. A difference in intercept (i.e. level change) implies an immediate change in outcomes at time of FMT program implementation. A difference in slope (i.e. slop change) implies a gradual effect of the FMT program over time.[28] Differences in intercepts and slopes were estimated based on the segmented logistic regression and tested using the Wald test. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, N.C.).

Results

Patient Characteristics

Among 430 hospital admissions with severe or fulminant CDI, 205 admissions occurred before (pre-FMT) and 225 after FMT program implementation (post-FMT). Patients from the two time periods were comparable except for a significant difference in the percentage of patients with IBD and median number of prior CDI episodes (Table 1)

Upon subgroup analysis, there were 199 hospitalizations for fulminant CDI; comparison of patient characteristics among 89 pre-FMT and 110 post-FMT hospitalizations only found a difference in the median number of prior CDI episodes (Table 2). In another subgroup consisting of 110 refractory CDI hospitalizations, comparison of 44 pre-FMT and 66 post-FMT patients revealed that the post-FMT group had a higher median number of prior CDI episodes and a lower proportion of mechanical ventilation and ICU stay (Table 3).

FMT Characteristics

A total of 50 patients received FMT due to refractory SFCDI. This amounted to 94 total FMTs delivered, 98% (92/94) via colonoscopy and 90.4% (85/94) with frozen stool via non-directed donor. Pseudomembranes were identified during 63.8% (60/94) of the FMTs. A median of 2 FMTs (IQR 1-2) was given to each patient who underwent this sequential protocol. FMT was also given to 21 other patients with non-refractory SFCDI for alternate indications including multiply recurrent CDI (n = 18), persistent ileus (n =2), and pseudomembranes during colonoscopy for restaging of IBD (n = 1).

Of the 16 patients with refractory SFCDI in the post-FMT period who did not undergo FMT, 6 underwent colectomy (5 survived, 1 died within 30 days), 3 continued with medical therapy and survived, and the remaining 7 died due to withdrawal of care or anatomic issues precluding delivery of FMT (obstructing distal colon cancer not allowing passage of an endoscope).

Outcomes

A summary of outcomes and comparison of pre-FMT to post-FMT time periods can be found in **Table 4**. Outcome trends over time are depicted in **Figure 1** for CDI-related mortality and **Figure 2** for CDI-related colectomy, where changes in level and slope for the effect of FMT program implementation are derived using the segmented logistic regression (SLR)

30-day CDI-Related Mortality

Rates of CDI-related mortality were significantly lower after FMT implementation in the SFCDI group (10.2% pre-FMT vs 4.4% post-FMT, *P* = .02), fulminant CDI group (21.3% pre-FMT vs 9.1% post-FMT, *P* = .015), and refractory SFCDI group (43.2% pre-FMT vs. 12.1% post-FMT, *P* < .001). After adjusting for the secular trend with SLR, differences in CDI-related mortality disappeared for SFCDI (Figure 1A) and fulminant CDI (Figure 1B). Neither level change nor slope change was statistically significant between the two time periods, although the figures suggest an increasing mortality rate before FMT program implementation and a decreasing trend afterwards.

The difference in CDI-related mortality between the pre- and post-FMT periods remained significant for the refractory SFCDI group (Figure 1C) after SLR analysis. The inpatient FMT program produced an immediate decrease in CDI-related mortality; the odds of mortality after introduction of the inpatient FMT program was 0.09 (95%CI: .01-.72, *P* = .023). There was a rising incidence of CDI-related mortality in the pre-FMT period compared to a decreasing incidence post-FMT, however the change in slope did not achieve significance (*P* = .07).

Among patients who received FMT for refractory SFCDI, 42% (21/50) were receiving non-CDI antibiotics at time of FMT. CDI-related mortality was not significantly different between the two groups (4.8% with vs 6.9% without non-CDI antibiotic use, *P* = .75).*CDI-Related Colectomy*

Comparing the pre-FMT to post-FMT time period, a lower proportion of hospitalizations had CDI-related colectomy in the SFCDI group (6.8% vs 2.7%, *P* = .041), fulminant subgroup (15.7% vs 5.5%, *P* = 0.017), and refractory SFCDI subgroup (31.8% vs 7.6% *P* = .001). Secular trends in CDI-related colectomy over time are depicted in Figure 2. There appeared to be a down-trending incidence of CDI-related colectomy prior to FMT program implementation. The downward trend continued after FMT

program implementation, leading to no significant differences in the slope or level change in any of the three CDI severity groups.

Other Secondary Outcomes

There were no significant changes in length of hospital stay or 30-day readmission rates between the pre- and post-FMT time periods across all CDI severity groups (Table 4).

Discussion

Our study showed a significantly lower 30-day CDI-related mortality rate in the time period after inpatient sequential FMT program became available for patients with SFCDI, including two subgroups consisting of fulminant CDI patients and refractory SFCDI patients. After adjusting for the underlying secular trend using segmented logistic regression, we found that the FMT program significantly decreased CDI-related mortality among patients with refractory SFCDI after its introduction in 2013. In the SFCDI group and fulminant CDI subgroup, CDI-related mortality demonstrated a similar rising trend pre-FMT and a downward trend post-FMT, however SLR did not yield significance in level or slope change. Our segmented regression analysis in the fulminant CDI subgroup was possibly hampered by a lack of power due to the small sample size of patients with CDI-related mortality. Specifically, our sample size could only provide 30% power for the observed effect in level change, and lower than 10% power for the observed effect in slope change.

Our findings reinforce the notion that FMT reduces mortality among severe CDI patients. In Hocquart and colleagues' recently published cohort of 111 hospitalized patients with severe CDI, 3-month mortality was 12.1% in those that received FMT and 42.2% in patients who received standard antibiotic therapy ($P < .0003$).[23] Our reported rates of mortality in severe CDI patients who did not receive FMT are much lower, likely explained by Hocquart's older patient group (median age 81 versus 61 years) and a different definition for mortality (3-month all-cause mortality versus 30-day CDI-related

mortality). We chose to define mortality within a 30-day post-procedure time frame to allow for direct comparison with the surgical literature. Patients with refractory SFCDI in our study would have otherwise been considered for surgical intervention due to failure of anti-CDI therapy; their rates of mortality compare favorably to previously published post-colectomy mortality rates.[10,11]

The rate of CDI-related colectomies was lower after FMT program implementation in the SFCDI, fulminant CDI, and refractory SFCDI groups. In a previous observational study, colectomies for severe CDI patients decreased after introduction of FMT despite a concurrent increase in CDI-related admissions.[24] We demonstrated a decreasing trend in the yearly rate of CDI-related colectomies even prior to introduction of FMT, a trend that likely reflects improved clinical management of severe CDI and changes in surgical concepts on when and whom to intervene.

This study supports the use of FMT for treatment of SFCDI, and indicates that patients with refractory SFCDI are likely to benefit most. More importantly, it presents FMT as an alternative to colectomy in cases of SFCDI where first-line anti-CDI antibiotics are partially or completely ineffective. Without FMT, failure of vancomycin or fidaxomicin in cases of refractory SFCDI traditionally leads to one of two unfavorable outcomes: continued medical management leading to an 80% mortality rate, or salvage colectomy resulting in post-surgical mortality rates in the 30-40% range.[2,29]

While randomized controlled trials are the gold standard for guideline recommendations, executing one would be difficult in such a vulnerable population for practical and ethical reasons; however, an adaptive trial approach may be appropriate. Emerging evidence suggests that FMT has an excellent safety profile and a noticeable benefit over standard medical therapy.[21,30,31] Although, guidelines suggest that patients with fulminant and refractory SFCDI should consider colectomy, the ideal window for surgical intervention is still ambiguous and there may be a role for FMT pre-colectomy. Prolonging surgery to optimize response to medical therapies could inadvertently facilitate deterioration

of the patient possibly beyond surgical repair, while premature surgical intervention would unnecessarily subject patients to high rates of morbidity post-colectomy. FMT could ameliorate this conundrum by serving as a potential cure for refractory SFCDI (thereby avoiding surgery completely). Or, even in cases where FMT is incompletely effective, FMT may also serve to quickly stabilize patients prior to surgery. Significant improvement in various clinical parameters (eg hemodynamics, vasopressor requirement, and leukocytosis) within 24 hours of receiving FMT has been observed in patients with SFCDI.[32] FMT could also fill the role of salvage therapy in patients whose age, comorbidities, or clinical status would otherwise be prohibitive of surgery.[33]

Beyond therapeutic potential, FMT in refractory SFCDI has other practical benefits over colectomy. Sequential FMT is more cost effective than colectomy in the treatment of SFCDI, decreasing overall treatment costs from $67,422 to $26,700.[34] Stool banks for donor material have eliminated the 1-2 week waiting time for donor stool screening, and the availability of FMT has blossomed such that 87.5% of the US population lives within 1 hour of an FMT provider.[35]

Further investigation is required to clearly define FMT's role and timing in the clinical course of severe and fulminant CDI. However, our study suggests that FMT should be offered to patients with severe and fulminant CDI that do not respond to a five-day course of anti-CDI antibiotics, and may be considered in lieu or prior to colectomy. Future studies will need to elucidate: a) the optimal FMT protocol including route of delivery, timing of first FMT, interval between sequential FMTs, role of pseudomembranes in directing therapy, b) the need of co-administration or continuation of anti-CDI antibiotic, c) the definition of FMT failure (after how many FMTs should one give up) and optimal timing of surgery, d) role and timing of FMT in prevention of CDI-associated end-organ failure such as ileus, toxic megacolon, and renal insufficiency, e) role of FMT to stabilize patients prior to undergoing colectomy, f) when to offer colectomy in patients that have not improved significantly after multiple rounds of FMT.

This study had several limitations. First, this is a single-center experience with skilled endoscopists and colorectal surgeons, leading to results that may not be generalizable. Second, this was an observational study with a small percentage of mortality or colectomy, which limited our ability to account for potential confounding factors when comparing differences in patient characteristics before and after FMT program. Third, during the course of our study, there were two significant changes to CDI diagnosis and treatment, though unlikely to be confounding factors. Prior to 2010, our institution tested for *C. difficile* using a two-step process consisting of *C. difficile* antigen glutamate dehydrogenase, followed by a confirmatory toxin A and B enzyme immunoassay (EIA), with reported sensitivity 41-92% and specificity 94-100%.[36] This was changed to PCR with increased sensitivity of 97.7% and specificity of 99.7%.[37] Despite this change and its theoretical improvement in timely delivery of anti-CDI antibiotics, rates of severe-complicated CDI and colectomy continued to rise afterwards. Additionally, new ACG guidelines for the management and treatment of *C. difficile* were also released in 2013,[5] coincident with the initiation of our inpatient FMT program. This could be interpreted as a potential confounding factor in our results. However, in comparison to the previously employed guidelines released by the IDSA in 2010,[38] the recommended treatment, antibiotic selection, and classification of severe, complicated, and/or refractory disease were not significantly different. Finally, analysis of patient characteristics for the refractory SFCDI group revealed that pre-FMT patients had an increased rate of ICU admissions and mechanical ventilation. Rapid stabilization of patients after receiving FMT likely accounted for some of this difference along with the significantly decreased rate of colectomy.

In summary, implementation of an inpatient FMT program was associated with significant decreases in CDI-related mortality in patients with refractory SFCDI even after accounting for background secular trends FMT should be considered in patients who fail maximal anti-CDI antimicrobial therapy who would otherwise be referred for surgical management.

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Table 1. Patient characteristics of severe or fulminant CDI hospitalizations.

	Total (N= 430)	Pre-FMT Program (N= 205)	Post-FMT Program (N= 225)	P Value
Age (years), mean (SD)	61.1 (16.5)	60.9 (14.9)	61.2 (17.9)	.82
Female, *n (%)*	212 (49.3%)	110 (53.7%)	102 (45.3%)	.085
Fulminant CDI, *n (%)*	199 (46.3%)	89 (43.4%)	110 (48.9%)	.26
Refractory CDI, *n (%)*	110 (25.6%)	44 (21.5%)	66 (29.3%)	.062
Maximum WBC, median (IQR)	22.8 (18.2 - 31.3)	22.8 (18.7 - 31.2)	22.7 (17.5 - 31.3)	.31
Minimum albumin, mean (SD)	2.3 (0.5)	2.3 (0.4)	2.4 (0.5)	.71
Number of Prior CDI episodes, median (IQR)	0.0 (0.0 - 1.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 1.0)	<.001
Charlson comorbidity score, mean (SD)	5.4 (3.0)	5.4 (3.0)	5.4 (3.1)	.81
IBD, *n (%)*	32 (7.4%)	8 (3.9%)	24 (10.7%)	.008
Immunosuppression, *n (%)*	90 (20.9%)	45 (22.0%)	45 (20.0%)	.62
Acute kidney injury, *n (%)*	204 (47.4%)	92 (44.9%)	112 (49.8%)	.31
Fever, *n (%)*	130 (30.2%)	58 (28.3%)	72 (32.0%)	.4
Hypotension, *n (%)*	181 (42.1%)	82 (40.0%)	99 (44.0%)	.4
Megacolon, *n (%)*	22 (5.1%)	8 (3.9%)	14 (6.2%)	.28
Vasopressor use, *n (%)*	78 (18.1%)	31 (15.1%)	47 (20.9%)	.12
Mental status change, *n (%)*	120 (27.9%)	52 (25.4%)	68 (30.2%)	.26
Ileus, *n (%)*	53 (12.3%)	25 (12.2%)	28 (12.4%)	.94
Mechanical ventilation, *n (%)*	83 (19.3%)	41 (20.0%)	42 (18.7%)	.73
ICU, *n (%)*	128 (29.8%)	56 (27.3%)	72 (32.0%)	.29

CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; ICU, intensive care unit; IBD, inflammatory bowel disease; WBC, white blood cell

Table 2. Patient characteristics of fulminant CDI hospitalizations.

	Total (N = 199)	Pre-FMT Program (N = 89)	Post-FMT Program (N = 110)	P Value
Age (years), mean (SD)	63.8 (15.2)	63.6 (13.4)	63.9 (16.6)	.86
Female, *n (%)*	100 (50.3%)	53 (59.6%)	47 (42.7%)	.018
Refractory CDI, *n (%)*	85 (42.7%)	36 (40.4%)	49 (44.5%)	.56
Maximum WBC, median (IQR)	24.6 (18.9 - 39.0)	25.4 (19.7 - 35.1)	24.6 (18.1 - 40.2)	.64
Minimum albumin, mean (SD)	2.4 (0.5)	2.4 (0.5)	2.4 (0.5)	.8
Number of Prior CDI episodes, median (IQR)	0.0 (0.0 - 1.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 2.0)	<.001
Charlson comorbidity score, mean (SD)	5.7 (2.9)	5.9 (3.0)	5.6 (2.9)	.35
IBD, *n (%)*	9 (4.5%)	3 (3.4%)	6 (5.5%)	.48
Immunosuppression, *n (%)*	44 (22.1%)	22 (24.7%)	22 (20.0%)	.43
Acute kidney injury, *n (%)*	159 (79.9%)	73 (82.0%)	86 (78.2%)	.5
Fever, *n (%)*	112 (56.3%)	49 (55.1%)	63 (57.3%)	.75
Hypotension, *n (%)*	181 (91.0%)	82 (92.1%)	99 (90.0%)	.6
Megacolon, *n (%)*	22 (11.1%)	8 (9.0%)	14 (12.7%)	.4
Vasopressor use, *n (%)*	78 (39.2%)	31 (34.8%)	47 (42.7%)	.26
Mental status change, *n (%)*	114 (57.3%)	51 (57.3%)	63 (57.3%)	1
Ileus, *n (%)*	53 (26.6%)	25 (28.1%)	28 (25.5%)	.68
Mechanical ventilation, *n (%)*	79 (39.7%)	40 (44.9%)	39 (35.5%)	.17
ICU, *n (%)*	112 (56.3%)	47 (52.8%)	65 (59.1%)	.37

CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; ICU, intensive care unit; IBD, inflammatory bowel disease; WBC, white blood cell

Table 3. Patient characteristics of refractory SFCDI hospitalizations.

	Total (N = 110)	Pre-FMT Program (N = 44)	Post-FMT Program (N = 66)	P Value
Age (years), mean (SD)	64.8 (16.3)	63.8 (13.3)	65.5 (18.2)	.59
Female, *n* (%)	60 (54.5%)	28 (63.6%)	32 (48.5%)	.12
Fulminant CDI, *n* (%)	85 (77.3%)	36 (81.8%)	49 (74.2%)	.35
Maximum WBC, median (IQR)	28.9 (20.7 - 42.8)	29.2 (20.7 - 41.8)	28.4 (20.7 - 43.2)	.88
Minimum albumin, mean (SD)	2.5 (0.5)	2.4 (0.5)	2.5 (0.6)	.18
Presence of Prior CDI episodes, median (IQR)	0.5 (0.0 - 2.0)	0.0 (0.0 - 1.0)	1.0 (0.0 - 3.0)	<.001
Charlson comorbidity score, mean (SD)	5.5 (2.9)	6.0 (3.0)	5.2 (2.8)	.14
IBD, *n* (%)	9 (8.2%)	1 (2.3%)	8 (12.1%)	.083
Immunosuppression, *n* (%)	21 (19.1%)	10 (22.7%)	11 (16.7%)	.43
Acute kidney injury, *n* (%)	79 (71.8%)	34 (77.3%)	45 (68.2%)	.3
Fever, *n* (%)	56 (50.9%)	23 (52.3%)	33 (50.0%)	.82
Hypotension, *n* (%)	76 (69.1%)	34 (77.3%)	42 (63.6%)	.13
Megacolon, *n* (%)	18 (16.4%)	7 (15.9%)	11 (16.7%)	.92
Vasopressor use, *n* (%)	36 (32.7%)	18 (40.9%)	18 (27.3%)	.14
Mental status change, *n* (%)	58 (52.7%)	28 (63.6%)	30 (45.5%)	.061
Ileus, *n* (%)	32 (29.1%)	16 (36.4%)	16 (24.2%)	.17
Mechanical ventilation, *n* (%)	41 (37.3%)	28 (63.6%)	13 (19.7%)	<.001
ICU, *n* (%)	64 (58.2%)	32 (72.7%)	32 (48.5%)	.012

CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; ICU, intensive care unit; IBD, inflammatory bowel disease; WBC, white blood cell

Table 4. Summary of outcomes in SFCDI and RCDI hospitalizations.

	Total	Pre-FMT Program	Post-FMT Program	P Value
Severe or Fulminant CDI				
CDI-related Mortality, *n* (%)	31 (7.2%)	21 (10.2%)	10 (4.4%)	.02
CDI-related Colectomy, *n* (%)	20 (4.7%)	14 (6.8%)	6 (2.7%)	.041
Length of Hospital Stay, Median (IQR)	13.0 (8.0 - 21.0)	13.0 (8.0 - 22.0)	13.0 (7.0 - 20.0)	.23
Readmission in 30 days, *n* (%)	30 (8.4%)	15 (8.8%)	15 (8.0%)	.77
Fulminant CDI				
CDI-related Mortality	29 (14.6%)	19 (21.3%)	10 (9.1%)	.015
CDI-related Colectomy	20 (10.1%)	14 (15.7%)	6 (5.5%)	.017
Length of Hospital Stay, Median (IQR)	14.0 (9.0 - 23.0)	14.0 (9.0 - 23.0)	13.0 (7.0 - 24.0)	.74
Readmission in 30 days	9 (6.1%)	4 (6.3%)	5 (6.0%)	1
Refractory SFCDI				
CDI-related Mortality, *n* (%)	27 (24.5%)	19 (43.2%)	8 (12.1%)	<.001
CDI-related Colectomy, *n* (%)	19 (17.3%)	14 (31.8%)	5 (7.6%)	.001
Length of Hospital Stay, Median (IQR)	13.5 (7.0 - 23.0)	15.0 (9.5 - 25.5)	12.0 (7.0 - 21.0)	.16
Readmission in 30 days, *n* (%)	5 (6.8%)	1 (4.0%)	4 (8.2%)	.66

CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplant.

Figure 1. Observed and predicted (dotted line) rates of CDI-related mortality before and after FMT program initiation. *(A)* Severe or Fulminant CDI. *(B)* Fulminant CDI. *(C)* Refractory SFCDI.

Figure 2. Observed and predicted (dotted line) rates of CDI-related colectomy before and after FMT program initiation. *(A)* Severe or Fulminant CDI. *(B)* Fulminant CDI. *(C)* Refractory SFCDI.